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    casein kinase I gamma-1 isoforms
    (CSNK1G1s) as modifiers of the p21 pathway and uses thereof in
    diagnosis, therapy and drug screening
    Francis-Lang, Helen: Friedman, Lori: Kidd, Thomas: Roche,
Siobhan; Zhang,
    Haiquang
    Exelixis, Inc., USA
PA
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    PCT Int. Appl., 69 pp.
    CODEN: PIXXD2
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The invention has designed a dominant loss of function screen to identify

genes that interact with the cyclin dependent kinase inhibitor

Drosophila. Casein kinase I gamma-1 isoform 3 (CSNK1G1) gene was identified as a modifier of the p21 pathway. Accordingly, vertebrate

orthologs of these modifiers, and preferably the human orthologs, casein

kinase I gamma-1 isoform (CSNK1G1) genes are attractive drag targets for

the treatment of pathologies associated with a defective p21 signaling

pathway, such as cancer. The invention also provides methods for utilizing these p21 modifier genes and polypeptides to identify candidate

therapeutic agents that can be used in the treatment of disorders associated

with defective p21 function.

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the treatment of disorders associated with defective p21 function.

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AN 1999268046 EMBASE

p21

DUPLICATE 1

Angiotensin II stimulates serine phosphorylation of the adaptor TΙ protein

Nck: Physical association with the serine/threonine kinases Pak1 and

casein kinase I.

Voisin L.; Larose L.; Meloche S. ΑIJ

S. Meloche, Centre de Recherche, Centre hospitalier Univ. de Montreal.

Campus Hotel-Dieu, 3850 St. Urbain, Montreal, Oue. H2W 1T8, Canada.

meloches@ere.umontreal.ca

SO Biochemical Journal, (1 Jul 1999) Vol. 341, No. 1, pp. 217-223. . Refs: 44

ISSN: 0264-6021 CODEN: BIJOAK

- CY United Kingdom
- DT Journal; Article
- FS 029 Clinical Biochemistry
- LA English
- SL English
- ED Entered STN: 12 Aug 1999
 - Last Updated on STN: 12 Aug 1999
- AB Nck is a small adaptor protein consisting exclusively of three SH3 domains
- and one SH2 domain. Nck is thought to have an important role in cell
- signalling by coupling receptor tyrosine kinases, via its SH2 domain, to
- downstream SH3-binding effectors. We report here that angiotensin II,
- working through the AT1 receptor subtype, stimulates the phosphorylation
- of Nck in rat aortic smooth muscle cells. Phosphopeptide mapping analysis
- revealed that Nck is phosphorylated on four peptides containing exclusively phosphoserine in quiescent cells. Treatment with andiotensin
- $\,$ II resulted in increased phosphorylation of these four peptides, without
- the appearance of new phosphopeptides. We show that Nck, via its ${\rm SH3}$
- domains, specifically binds three major phosphoproteins of 95, 82 and 66
- kDa both in vitro and in intact cells. Notably, the phosphorylation of
- these Nck-binding proteins was found to increase in parallel with that of
- Nck on stimulation by angiotensin II. One candidate for the 66 $\ensuremath{\text{kDa}}$
- phosphoprotein is the serine/threonine kinase p21-activated kinase 1 (Pakl), which was found to form a stable complex with Nck in
- aortic smooth muscle cells. We have also identified the $\gamma 2$ isoform
- of casein kinase I as another protein kinase that associates with Nok in
- these cells. These findings indicate that Nck is a target of G-protein-coupled receptors and suggest a role for Pak1 and casein
 - kinase I-.gamma.2 in downstream signalling or regulation of the AT1 receptor.

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